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Abstract: Background: Gliomatosis cerebri (GC) is a diffuse infiltrating glial tumor with involvement of at least 3 cerebral lobes. There are only few data on the efficacy of initial chemotherapy in patients with GC. Patients and Methods: In 3 neurooncological centers, patients with newly diagnosed GC who had received procarbazine (60 mg/m²), days 8-21/56) and CCNU (110 mg/m²), day 1/56) chemotherapy (PC) as initial treatment were analyzed for progression-free survival, overall survival and toxicity. Results: Twelve patients (median age 46 years, range 27-72) were analyzed. The median progression-free survival and the median overall survival were 16 and 37 months. Grade 3 or 4 hematotoxicity was observed in 3 of 12 patients (25%). Conclusions: These data support the efficacy of PC chemotherapy in newly diagnosed GC. Initial PC chemotherapy should be considered as a treatment option and evaluated in larger clinical trials.

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Procarbazine and CCNU as Initial Treatment in Gliomatosis Cerebri

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Key Words

Gliomatosis cerebri • CCNU • Procarbazine • Chemotherapy • Brain tumors

Abstract

Background: Gliomatosis cerebri (GC) is a diffuse infiltrating glial tumor with involvement of at least 3 cerebral lobes. There are only few data on the efficacy of initial chemotherapy in patients with GC. **Patients and Methods:** In 3 neurooncological centers, patients with newly diagnosed GC who had received procarbazine (60 mg/m², days 8–21/56) and CCNU (110 mg/m², day 1/56) chemotherapy (PC) as initial treatment were analyzed for progression-free survival, overall survival and toxicity. **Results:** Twelve patients (median age 46 years, range 27–72) were analyzed. The median progression-free survival and the median overall survival were 16 and 37 months. Grade 3 or 4 hematotoxicity was observed in 3 of 12 patients (25%). **Conclusions:** These data support the efficacy of PC chemotherapy in newly diagnosed GC. Initial PC chemotherapy should be considered as a treatment option and evaluated in larger clinical trials.

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Introduction

Gliomatosis cerebri (GC) is a glial tumor with a diffuse growth pattern consisting of exceptionally extensive infiltration of the central nervous system and with involvement of at least 3 cerebral lobes [1]. Its relationship with diffuse low-grade gliomas and highly infiltrative malignant gliomas has remained unclear. No standard treatment has been established. Due to the large extent of tumor infiltration, the surgical options are limited. Extensive field radiotherapy can lead to clinical and radiological stabilization or improvement, but requires high doses of 45 Gy and more and, therefore, carries the risk of neurotoxicity [2, 3]. Efficacy data for primary chemotherapy are scarce and restricted to retrospective analyses. After biopsy, temozolomide (TMZ) or PCV chemotherapy (procarbazine, CCNU, vincristine) lead to a median progression-free survival (mPFS) of 13–16 months and a median overall survival (mOS) of 25–27 months [3, 4]. In a small patient series, we had some indications for the efficacy of procarbazine and CCNU (PC) in patients with GC [5]. On this basis, we continued to treat GC patients with PC. In most patients we omitted vincristine, since vincristine does not penetrate the blood brain barrier [6]. Here, we present the analysis of 12 patients who had received PC(V) chemotherapy in the pilot phase of a German multicenter trial.

Table 1. Patient characteristics

Patients	12
PC	9 (75)
PCV	3 (25)
Demographic data	
Males	5 (42)
Females	7 (58)
Age, years	
Median	46
Range	27–62
KPS	
Median	80
Range	60–90
Treatment before inclusion	
Neurosurgery	12
Partial resection	2 (16)
Biopsy	10 (84)
PC(V) cycles	
Median	4
Range	1–7

Figures in parentheses are percentages.

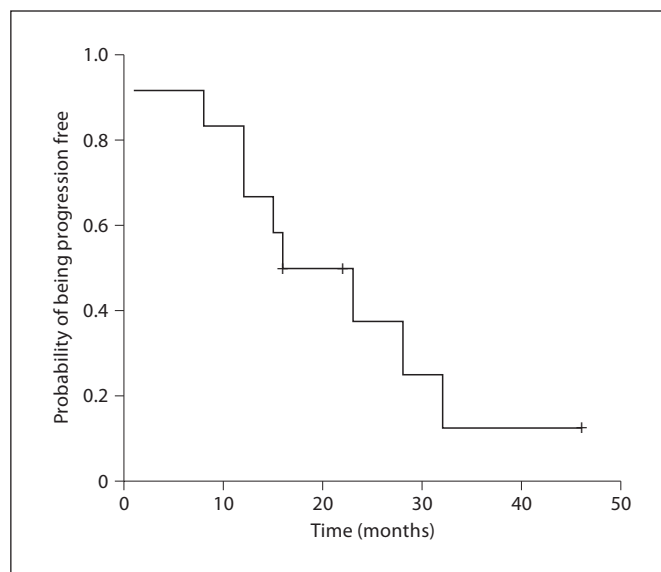
KPS = Karnofsky performance status.

Patients and Methods

For this analysis, patients with newly diagnosed GC who received PC or PCV chemotherapy were retrieved from the institutional data bases of the Department of Neurology, University of Tübingen, Tübingen, the Division of Clinical Neurooncology, Department of Neurology, University of Bonn, and the Department of Neurosurgery, University of Mainz, Mainz, Germany. Informed consent for treatment was obtained from each patient before therapy.

GC was diagnosed according to the following criteria: (1) T₂- or fluid-attenuated inversion recovery (FLAIR)-weighted MRI showing a diffuse infiltrative process involving more than 2 different lobes; (2) histological confirmation of a focal glial neoplastic lesion.

The PC regimen was administered with 110 mg/m² CCNU on day 1 and with 60 mg/m² procarbazine on days 8–21 of 56-day courses. Tumor response was assessed by cranial MRI in subsequent courses according to the following criteria: a partial response (PR) required a reduction in the contrast-enhancing tumor mass by 50% and/or a reduction in the tumor mass on FLAIR sequences by at least 25% (without progression of the contrast-enhancing tumor mass); progressive disease (PD) was diagnosed in case of a more than 25% increase in the contrast-enhancing tumor mass and/or tumor mass on FLAIR sequences. All other constellations between PR and PD were considered stable disease (SD). The diagnosis of PR and SD also required stable or improved neurological status. PFS and OS were calculated from the first dose of CCNU until progression or death, respectively. Survival data were analyzed according to the Kaplan-Meier method using the SPSS software version 12.0.1.

**Fig. 1.** PFS in the 12 patients with GC.

Results

Patient and Treatment Characteristics

Twelve patients with newly diagnosed GC were treated with PC between December 2001 and December 2006. The patient characteristics are given in table 1. Ten patients had a biopsy only and 2 patients had a partial resection. Two patients had grade 2 oligodendroglioma and 10 patients had grade 2 diffuse astrocytoma as histology of the location where the biopsy has been taken from. Nine patients were treated with PC and 3 patients were treated with PCV. A total of 43 courses of PC and 9 courses of PCV were administered. The median number of courses per patient was 4. One patient had only 1 course, and another patient received the maximum of 7 courses.

Efficacy and Toxicity of PC Chemotherapy

All patients were followed until tumor progression and death. SD was seen in 11 of 12 patients (92%) and prevailed in all of them for at least 2 months. There were no CR or PR. PFS and OS are shown in figures 1 and 2. mPFS was 16 months (95% CI 5–27; fig. 1). The PFS rates at 12 and 24 months were 83 and 38%, respectively. mOS was 37 months (95% CI 33–41; fig. 2).

Grade 3 or 4 hematologic toxicity was seen in 3 patients (25%) leading to a 25% reduction in the dose of PC. During procarbazine treatment, allergic skin reaction leading to treatment discontinuation occurred in 1 patient (8%).

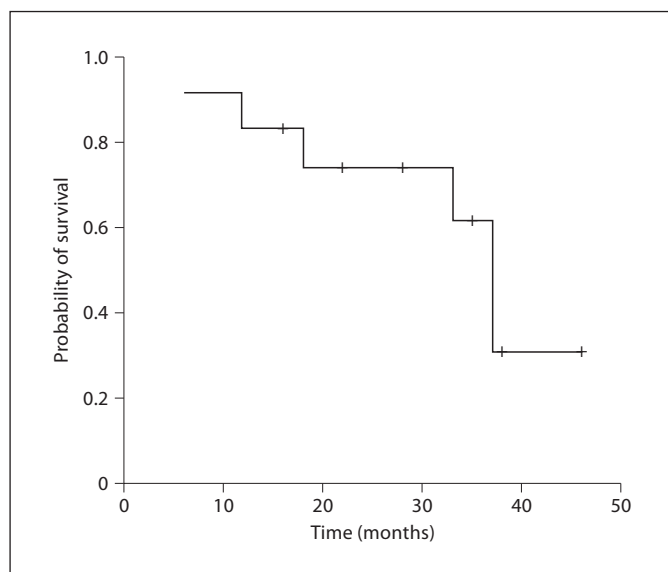


Fig. 2. OS in the 12 patients with GC.

Salvage Therapy

So far, 9 patients had recurrent disease and 8 of them received salvage therapy. Six of 8 patients were treated with involved-field radiotherapy (50.4–60 Gy) and showed an mPFS of 5 months. One patient with radiotherapy and concurrent TMZ was stable for 3 months. Another patient received TMZ at first recurrence (200 mg/m², on day 5/28) and had SD for at least 5 months. Four patients who had radiotherapy at first relapse were evaluable for third-line treatment with TMZ (2 of them with a dose-intensive regimen). The median time to third progression was 2 months.

Discussion

This analysis suggests that PC chemotherapy may be effective in patients with newly diagnosed GC. PC leads to a comparably long median survival of 37 months. Almost 40% of patients showed long-term stabilization for more than 2 years upon PC therapy. Radiotherapy, which may be an alternative treatment option, had been less active in previous studies, with median survival times ranging between 11 and 24 months [2, 7–9]. In the most comprehensive analysis of GC patients including 41 patients treated with radiotherapy alone, the retrospective comparison of patients receiving radiotherapy with patients not receiving radiotherapy did not reveal a prolongation of survival for those receiving radiotherapy, thus ques-

tioning its value [10]. In our series, second-line radiotherapy was also comparably ineffective with a short mPFS of 5 months. Another problem with radiotherapy as the primary treatment strategy is the increased risk of leukoencephalopathy with cognitive dysfunction due to the large-field radiotherapy which is needed for this highly infiltrative tumor [11].

In contrast to radiotherapy, the comprehensive retrospective analysis provided by Taillibert et al. [10] showed that the application of chemotherapy was a highly significant prognostic factor. With primary TMZ chemotherapy, PFS was 13 months [4]. Soffietti et al. [12] showed a PFS of 9 months for 46 patients who received TMZ as primary or secondary therapy. Also, Levin et al. [3] demonstrated no significant difference between PCV- (n = 17) and TMZ-treated (n = 46) patients in either mPFS (16 months) or mOS (26 months). Our data add valuable information of 12 more patients and appear competitive with a PFS of 16 months and an mOS of 37 months. There was no strong selection of patients with good prognostic factors such as young age or high Karnofsky performance status in our case series. One could argue that our analysis only comprises patients with local grade 2 histology which was a positive prognostic factor in some studies [4, 10]. However, in the study of Levin et al. [3], no correlation between survival parameters and tumor grade was found. The comparably long OS in our cohort may be due to the high rate of patients receiving second-line therapy or even multiple salvage therapies.

In conclusion, the PC chemotherapy exhibits encouraging efficacy in newly diagnosed GC. Initial PC chemotherapy should be considered as a treatment option and evaluated in larger clinical trials. A German multicenter trial (NOA-05) investigating this concept is already recruiting.

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